REFERENCE BL

PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 7 : C07D 498/04, A61K 31/535 // (C07D 498/04, 209:00, 265:00)

A1

(11) International Publication Number: **WO 00/17207**

(43) International Publication Date: 30 March 2000 (30.03.00)

(21) International Application Number: PCT/EP99/06780

(22) International Filing Date: 14 September 1999 (14.09.99)

(30) Priority Data:
9820294.8 17 September 1998 (17.09.98) GB

(71) Applicant *(for all designated States except US)*: SMITHKLINE BEECHAM P.L.C. [GB/GB]; New Horizons Court, Brentford, Middlesex TW8 9EP (GB).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: HOSSNER, Frank [GB/GB]; (GB). RYAN, David, Austin [GB/GB]; New Frontiers Science Park South, Third Avenue, Harlow, Essex CM19 5AW (GB).

(74) Agent: GARRETT, Michael; SmithKline Beecham, Two New Horizons Court, Brentford, Middlesex TW8 9EP (GB).

(81) Designated States: CA, JP, US, European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).

Published
With international search report.

(54) Title: 3,4–DIHYDRO –N–[[1–(3 –HYDROXYBUTYL) –4–PIPERIDINYL] METHYL] –2H–[1,3] OXAZINO[3, 2–A]INDOLE –10–CARBOXAMIDE AS 5–HT(4) RECEPTOR ANTAGONIST

(57) Abstract

3,4–Dihydro–*N*–*[[1*–*(3*–*hydroxybutyl*–4–piperidinyl]methyl]*–2*H*–[1.3]oxazino[3,2–*a*]indole–10–carboxamide and its use as 5–HT_4 receptor antagonist for example in the treatment or prophylaxis of gastrointestinal disorders, cardiovascular disorders and CNS disorders.

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	ES	Spain	LS	Lesotho	SI	Slovenia
AM	Armenia	FI	Finland	LT	Lithuania	SK	Slovakia
AT	Austria	FR	France	LU	Luxembourg	SN	Senegal
AU	Australia	GA	Gabon	LV	Latvia	SZ	Swaziland
AZ	Azerbaijan	GB	United Kingdom	MC	Monaco	TD	Chad
BA	Bosnia and Herzegovina	GE	Georgia	MD	Republic of Moldova	TG	Togo
BB	Barbados	GH	Ghana	MG	Madagascar	TJ	Tajikistan
BE	Belgium	GN	Guinea	MK	The former Yugoslav Republic of Macedonia	TM	Turkmenistan
BF	Burkina Faso	GR	Greece			TR	Turkey
BG	Bulgaria	HU	Hungary	ML	Mali	TT	Trinidad and Tobago
BJ	Benin	IE	Ireland	MN	Mongolia	UA	Ukraine
BR	Brazil	IL	Israel	MR	Mauritania	UG	Uganda
BY	Belarus	IS	Iceland	MW	Malawi	US	United States of America
CA	Canada	IT	Italy	MX	Mexico	UZ	Uzbekistan
CF	Central African Republic	JP	Japan	NE	Niger	VN	Viet Nam
CG	Congo	KE	Kenya	NL	Netherlands	YU	Yugoslavia
CH	Switzerland	KG	Kyrgyzstan	NO	Norway	ZW	Zimbabwe
CI	Côte d'Ivoire	KP	Democratic People's Republic of Korea	NZ	New Zealand		
CM	Cameroon			PL	Poland		
CN	China	KR	Republic of Korea	PT	Portugal		
CU	Cuba	KZ	Kazakstan	RO	Romania		
CZ	Czech Republic	LC	Saint Lucia	RU	Russian Federation		
DE	Germany	LI	Liechtenstein	SD	Sudan		
DK	Denmark	LK	Sri Lanka	SE	Sweden		
EE	Estonia	LR	Liberia	SG	Singapore		

3,4-DIHYDRO-N-[[1-(3-HYDROXYBUTYL)-4-PIPERIDINYL]METHYL]-2H-[1,3]OXAZINO[3,2-A] INDOLE-10-CARBOXAMIDE AS 5-HT(4) RECEPTOR ANTAGONIST

This invention relates to novel compounds having pharmacological activity, to a process for their preparation and to their use as pharmaceuticals.

EP-A-429984 (Nisshin Flour Milling Co., Ltd.) describes indole derivatives having 5-HT_3 receptor antagonist activity.

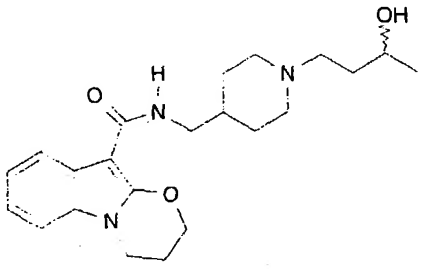
European Journal of Pharmacology 146 (1988), 187-188, and Naunyn-Schmiedeberg's Arch. Pharmacol. (1989) 340:403-410, describe a non classical 5-hydroxytryptamine receptor, now designated the 5-HT_4 receptor, and that ICS 205-930, which is also a 5-HT_3 receptor antagonist, acts as an antagonist at this receptor.

WO 91/16045 (SmithKline and French Laboratories Limited) describes the use of cardiac 5-HT_4 receptor antagonists in the treatment of atrial arrhythmias and stroke.

EP-A-501322 (Glaxo Group Limited) describes indole derivatives having 5-HT_4 antagonist activity.

WO93/18036 (SmithKline Beecham plc) describes certain condensed indole derivatives having 5-HT_4 receptor antagonist activity. Among these derivatives the compound N-[(1-^{n}butyl-4-piperidyl)methyl]-3,4-dihydro-2H-[1,3]oxazino[3,2-a]indole-10-carboxamide has been found to have potent 5-HT_4 receptor antagonist activity and to be of therapeutic value in the treatment of irritable bowel syndrome. In the evaluation of this compound we have found that one of its metabolites, namely the compound of formula (I) below, itself has potent 5-HT_4 receptor antagonist activity.

Accordingly, the present invention provides 3,4-dihydro-*N*-[[1-(3-hydroxybutyl)-4-piperidinyl]methyl]-2*H*-[1,3]oxazino[3,2-*a*]indole-10-carboxamide i.e. the compound of formula (I), or a pharmaceutically acceptable salt thereof:



(I)

According to a further feature of the present invention we provide the compound of formula (I) and its pharmaceutically acceptable salts in synthetic form, i.e. not produced by a biological process from its metabolic precursor referred to above. The compound of formula (I) is also preferably in pharmaceutically acceptable form. By pharmaceutically acceptable form is meant, *inter alia*, of a pharmaceutically acceptable level of purity excluding normal pharmaceutical additives such as diluents and carriers, and including no material considered toxic at normal dosage levels. A pharmaceutically acceptable level of purity will generally be at least 50% excluding normal pharmaceutical additives, preferably 75%, more preferably 90% and still more preferably 95%. One preferred pharmaceutically acceptable form is the crystalline form, including such form in a pharmaceutical composition.

The pharmaceutically acceptable salts of the compound of the formula (I) include acid addition salts with conventional acids such as hydrochloric, hydrobromic, boric, phosphoric, sulphuric acids and pharmaceutically acceptable organic acids such as acetic, tartaric, maleic, citric, succinic, benzoic, ascorbic, methanesulphonic, α-keto glutaric, α-glycerophosphoric, and glucose-1-phosphoric acids.

Examples of pharmaceutically acceptable salts include quaternary derivatives of the compound of formula (I) such as the compounds quaternised by compounds R_X-T wherein R_X is C_{1-6} alkyl, phenyl-C_{1-6} alkyl or C_{5-7} cycloalkyl, and T is a radical corresponding to an anion of an acid. Suitable examples of R_X include methyl, ethyl and *n*- and *iso*-propyl; and benzyl and phenethyl. Suitable examples of T include halide such as chloride, bromide and iodide.

Examples of pharmaceutically acceptable salts also include internal salts such as N-oxides.

The compound of the formula (I) and its pharmaceutically acceptable salts, (including quaternary derivatives and N-oxides) may also form pharmaceutically acceptable solvates, such as hydrates, which are included wherever the compound of formula (I) or a salt thereof is herein referred to. The compound of formula (I) is a racemate. The present invention also covers the corresponding individual (+) and (-) enantiomers.

The compound of formula (I) may be prepared as described in the Example below or by other conventional coupling of the indole moiety with the piperidine side chain. for example by reacting 1-(3-(protected)hydroxybutyl)-4-piperidinyl methylamine with methyl 3,4-dihydro-2H-[1,3]oxazino[3,2-a]indole-10-carboxylate and subsequently removing the protecting group: the 3-hydroxybutyl group is

advantageously protected by an appropriate silyl or benzyl group. Suitable methods are as described in GB 2125398A (Sandoz Limited), GB 1593146A and EP-A-36269 (Beecham Group p.l.c.), EP-A-429984 (Nisshin Flour Milling Co.) and EP-A-328200 (Merck Sharp & Dohme Limited). Reference is also made to EP-A-501322 (Glaxo Group Limited). It will be appreciated that the formation of O- containing ring may be carried out before or after coupling.

The compounds of the present invention are 5-HT_4 receptor antagonists and it is thus believed may generally be used in the treatment or prophylaxis of gastrointestinal disorders, cardiovascular disorders and CNS disorders.

They are of potential interest in the treatment of irritable bowel syndrome (IBS), in particular the diarrhoea aspects of IBS, i.e., these compounds block the ability of 5-HT to stimulate gut motility via activation of enteric neurones. In animal models of IBS, this can be conveniently measured as a reduction of the rate of defaecation. They are also of potential use in the treatment of urinary incontinence which is often associated with IBS.

They may also be of potential use in other gastrointestinal disorders, such as those associated with upper gut motility, and as antiemetics. In particular, they are of potential use in the treatment of the nausea and gastric symptoms of gastro-oesophageal reflux disease and dyspepsia. Antiemetic activity is determined in known animal models of cytotoxic-agent/radiation induced emesis.

Specific cardiac 5-HT_4 receptor antagonists which prevent atrial fibrillation and other atrial arrhythmias associated with 5-HT, would also be expected to reduce occurrence of stroke (see A.J. Kaumann 1990, Naumyn-Schmiedeberg's Arch. Pharmacol. 342, 619-622, for appropriate animal test method).

It is believed that platelet-derived 5-HT induces atrial arrhythmias which encourage atrial fibrillation and atrial disorders are associated with symptomatic cerebral and sytemic embolism. Cerebral embolism is the most common cause of ischaemic stroke and the heart the most common source of embolic material. Of particular concern is the frequency of embolism associated with atrial fibrillation.

Anxiolytic activity is likely to be effected via the hippocampus (Dumuis *et al* 1988, Mol Pharmacol., 34, 880-887). Activity may be demonstrated in standard animal models, the social interaction test and the X-maze test.

Migraine sufferers often undergo situations of anxiety and emotional stress that precede the appearance of headache (Sachs, 1985, Migraine, Pan Books, London). It has also been observed that during and within 48 hours of a migraine attack, cyclic AMP levels are considerably increased in the cerebrospinal fluid (Welch *et al.*, 1976, Headache 16, 160-167). It is believed that a migraine, including the prodomal phase and the associated increased levels of cyclic AMP are related to stimulation of 5-HT_4 receptors, and hence that administration of a 5-HT_4 antagonist is of potential benefit in relieving a migraine attack.

The invention also provides a pharmaceutical composition comprising the compound of formula (I), or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

Such compositions are prepared by admixture and are usually adapted for enteral such as oral, nasal or rectal, or parenteral administration, and as such may be in the form of tablets, capsules, oral liquid preparations, powders, granules, lozenges, reconstitutable powders, nasal sprays, suppositories, injectable and infusable solutions or suspensions. Sublingual or transdermal administration is also envisaged. Orally administrable compositions are preferred, since they are more convenient for general use.

Tablets and capsules for oral administration are usually presented in a unit dose, and contain conventional excipients such as binding agents, fillers, diluents, tabletting agents, lubricants, disintegrants, colourants, flavourings, and wetting agents. The tablets may be coated according to well known methods in the art, for example with an enteric coating.

Suitable fillers for use include cellulose, mannitol, lactose and other similar agents. Suitable disintegrants include starch, polyvinylpolypyrrolidone and starch derivatives such as sodium starch glycollate. Suitable lubricants include, for example, magnesium stearate.

Suitable pharmaceutically acceptable wetting agents include sodium lauryl sulphate. Oral liquid preparations may be in the form of, for example, aqueous or oily suspensions, solutions, emulsions, syrups, or elixirs, or may be presented as a dry product for reconstitution with water or other suitable vehicle before use. Such liquid preparations may contain conventional additives such as suspending agents, for example sorbitol, syrup, methyl cellulose, gelatin, hydroxyethylcellulose, carboxymethylcellulose, aluminium stearate gel or hydrogenated edible fats, emulsifying agents, for example lecithin, sorbitan monooleate, or acacia; non-aqueous

vehicles (which may include edible oils), for example, almond oil, fractionated coconut oil, oily esters such as esters of glycerine, propylene glycol, or ethyl alcohol; preservatives, for example methyl or propyl p-hydroxybenzoate or sorbic acid, and if desired conventional flavouring or colouring agents.

Oral liquid preparations are usually in the form of aqueous or oily suspensions, solutions, emulsions, syrups, or elixirs or are presented as a dry product for reconstitution with water or other suitable vehicle before use. Such liquid preparations may contain conventional additives such as suspending agents, emulsifying agents, non-aqueous vehicles (which may include edible oils), preservatives, and flavouring or colouring agents.

The oral compositions may be prepared by conventional methods of blending, filling or tabletting. Repeated blending operations may be used to distribute the active agent throughout those compositions employing large quantities of fillers. Such operations are, of course, conventional in the art.

For parenteral administration, fluid unit dose forms are prepared containing a compound of the present invention and a sterile vehicle. The compound, depending on the vehicle and the concentration, can be either suspended or dissolved. Parenteral solutions are normally prepared by dissolving the compound in a vehicle and filter sterilising before filling into a suitable vial or ampoule and sealing. Advantageously, adjuvants such as a local anaesthetic, preservatives and buffering agents are also dissolved in the vehicle. To enhance the stability, the composition can be frozen after filling into the vial and the water removed under vacuum.

Parenteral suspensions are prepared in substantially the same manner except that the compound is suspended in the vehicle instead of being dissolved and sterilised by exposure of ethylene oxide before suspending in the sterile vehicle. Advantageously, a surfactant or wetting agent is included in the composition to facilitate uniform distribution of the compound of the invention.

The invention further provides a method of treatment of irritable bowel syndrome, gastro-oesophagal reflux disease, dyspepsia, atrial arrhythmias and stroke, anxiety and/or migraine in mammals, such as humans, which comprises the administration of an effective amount of the compound of the formula (I) or a pharmaceutically acceptable salt thereof. In particular, the method comprises treatment of IBS or atrial arrhythmias and stroke.

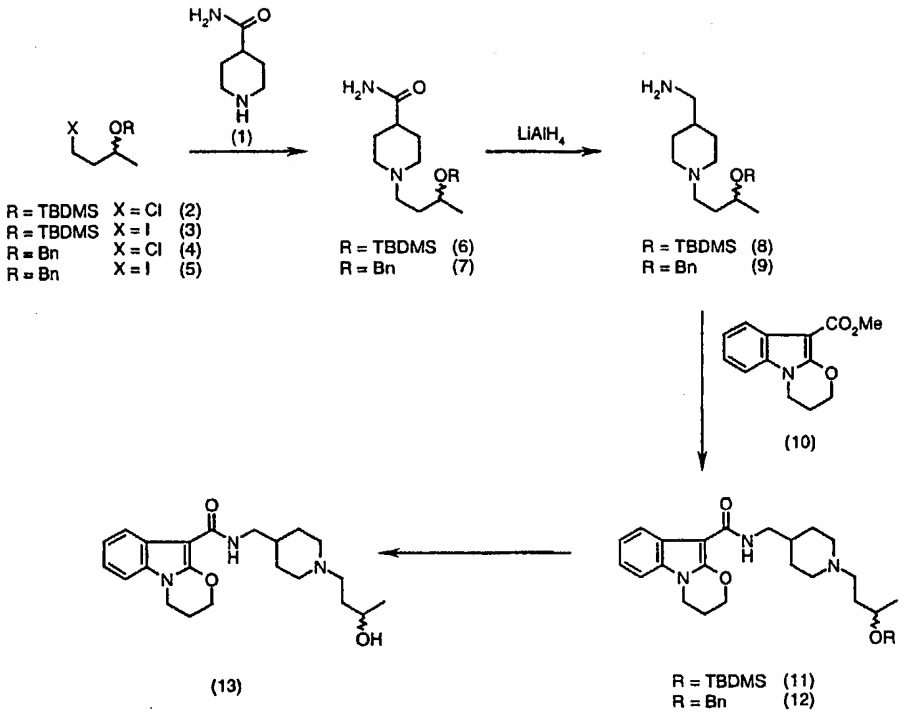
An amount effective to treat the disorders hereinbefore described depends on the relative efficacies of the compounds of the invention, the nature and severity of the disorder being treated and the weight of the mammal. However, a unit dose for a 70 kg adult will normally contain 0.05 to 1000 mg for example 0.5 to 500 mg, of the compound of the invention. Unit doses may be administered once or more than once a day, for example, 2, 3 or 4 times a day, more usually 1 to 3 times a day, that is in the range of approximately 0.0001 to 50 mg/kg/day, more usually 0.0002 to 25 mg/kg/day.

No adverse toxicological effects are indicated within the aforementioned dosage ranges.

The invention also provides the compound of formula (I) or a pharmaceutically acceptable salt thereof for use as an active therapeutic substance, in particular for use as a 5-HT_4 receptor antagonist in the treatment of the disorders hereinbefore described.

The invention also provides the use of the compound of formula (I) in the manufacture of a medicament for use as a 5-HT_4 receptor antagonist in the treatment of the disorders hereinbefore described.

The following Example illustrates the preparation of the compound of formula (I) by two methods, as indicated in the scheme below:



(1) 4-piperidinecarboxamide

(2) (3-chloro-1-methylpropoxy)(1,1-dimethylethyl)dimethylsilane

(3) (1,1-dimethylethyl)(3-iodo-1-methylpropoxy)dimethylsilane

(4) 1-[(3-chloro-1-methylpropoxy)methyl]benzene

(5) 1-[(3-iodo-1-methylpropoxy)methyl]benzene

(6) 1-[3-[[(1,1-dimethylethyl)dimethylsilyl]oxy]butyl]-4-piperidinecarboxamide

(7) 1-[3-(phenylmethoxy)butyl]-4-piperidinecarboxamide

(8) 1-[3-[[(1,1-dimethylethyl)dimethylsilyl]oxy]butyl]-4-piperidinemethanamine

(9) 1-[3-(phenylmethoxy)butyl]-4-piperidinemethanamine

(10) methyl 3,4-dihydro-2*H*-[1,3]oxazino[3,2-*a*]indole-10-carboxamide

(11) *N*-[[1-[3-[[(1,1-dimethylethyl)dimethylsilyl]oxy]butyl]-4-piperidinyl]methyl]-3,4-dihydro-2*H*-[1,3]oxazino[3,2-*a*]indole-10-carboxamide

(12) 3,4-dihydro-*N*-[[1-[3-(phenylmethoxy)butyl]-4-piperidinyl]methyl]- 2*H*-[1,3]oxazino[3,2-*a*]indole-10-carboxamide

(13) 3,4-dihydro-*N*-[[1-(3-hydroxybutyl)-4-piperidinyl]methyl]-2*H*-[1,3]oxazino[3,2-*a*]indole-10-carboxamide

Method 1

Preparation of (2)

To 4-chlorobutan-2-ol (15g, 0.14M) dissolved in DMF (50 ml) was added imidazole (20.7g, 0.3M), and TBDMS chloride (22.9g, 0.15M). The solution formed was stirred under nitrogen for 16 hr., quenched with water (200 ml) and extracted with ethyl acetate (2 x 100 ml). The combined organic extracts were washed with water (5 x 50 ml), brine, dried over sodium sulphate, filtered and evaporated under reduced pressure to give an oil. Purification by Kugelrohr distillation gave (2) as an oil, 27.4g (89%).

^{1}H NMR ($CDCl_3$) δ: 3.92 ((m, 1H), 3.32 (m, 2H), 1.76 (m, 2H), 1.08 (d, 3H), 0.81 (s, 9H), 0.00 (s, 6H).

Preparation of (3)

A solution of (2) (10g, 44.9 mmol) and sodium iodide (16.6g, 111 mmol) in acetone (50 ml) was heated under reflux for 45 hr. The mixture was allowed to cool, filtered, and the filtrate evaporated under reduced pressure. The residue was extracted with diethyl ether (5 x 50 ml) and the combined extracts evaporated under reduce pressure to give (3) as an oil, 13.5g (96%).

^{1}H NMR ($CDCl_3$) δ: 3.80 (m, 1H), 3.12 (m, 2H), 1.82 (m, 2H), 1.08 (d, 3H), 0.77 (s, 9H), 0.01 (d, 6H)

Preparation of (6)

A suspension of *iso*-nipecotamide (1) (3g, 23.4 mmol), (3) (8.2g, 26.2 mmol) and anhydrous potassium carbonate (9.7g, 70 mmol) in toluene (120 ml) was heated at 90°C for 17 hours, then heated under reflux for 5 hr. The reaction mixture was allowed to cool, filtered, and the filtrate washed with water (4 x 30 ml), brine, dried over sodium sulphate, filtered, and evaporated under reduced pressure to an oil which solidified on standing, obtaining (6), 7.9g (108%). This material was used without further purification.

^{1}H NMR ($CDCl_3$) δ: 5.8-5.6 (d, broad, 2H), 3.8 (m, 1H), 2.9 (m, 2H), 2.4-1.5 (m, 11H), 1.1 (d, 3H), 0.82 (s, 9H), 0.01 (s, 6H)

^{13}C NMR (CD_3OD) δ: 181, 68, 56, 54, 43, 37, 29, 26, 24, 19, -4.2, -4.6

m.s. 315.2 (ES^+, M+1)

Preparation of (8)

To a suspension of $LiAlH_4$ (11.6g, 0.24M) in THF (115 ml) at 5°C was added (6) (7g, 0.022M) dissolved in THF (65 ml) dropwise over 1 hour. The mixture was allowed to warm up to room temperature, stirred for 30 minutes and then heated at reflux for 1 hour. The reaction mixture was cooled to ambient temperature, then sodium hydroxide solution (7.9M, 22.5 ml) was added dropwise over 2 hours. The resulting mixture was filtered through celite, the celite washed with THF (4 x 50 ml), and the combined filtrate and washes evaporated under reduced pressure to give (8) as an oil, 3.1g (46%).

^1H NMR ($CDCl_3$) δ: 3.8 (m, 1H), 3.1-1.1 (m, 20H), 0.8 (s, 9H), 0.0 (s, 6H)

m.s. 301.3 (ES^+, M+1)

Preparation of (11)

Trimethylaluminium (2M in toluene, 8.2 ml) was diluted with toluene (8 ml) and the solution cooled to 0°C. A solution of (8) (3g, 10 mmol) in toluene (25 ml) was added over 3 minutes, followed by SB-224908 (3.4g, 14.7 mmol). The mixture was heated at reflux for 5 hours, then allowed to cool, and sodium hydroxide solution (10% w/w, 18 ml) was added dropwise. The toluene layer was washed with water, brine, dried over sodium suphate, filtered, and evaporated under reduced pressure to give an oil. This was purified by flash chromatography on silica (eluting with 0-1% MeOH in $CHCl_3$) obtaining 2g (40%) (11) as a solid.

^1H NMR ($CDCl_3$, 400 MHz) δ: 8.3 (m 1H), 7.2-7.1 (m, 3H), 6.5 (t, 1H, NH), 4.5 (t, 2H), 4.1 (t, 2H), 3.8 (m, 1H), 3.3 (t, 2H), 2.9 (m, 2H), 2.3 (m, 4H), 1.9 (m, 2H), 1.7 (m, 2H), 1.6 (m, 2H), 1.4 (m, 2H), 1.1 (d, 3H), 0.9 (s, 9H), 0.04 (s, 6H).

^{13}C ($CDCl_3$) δ: 165, 149, 131, 125, 122, 121, 120, 107, 89, 67, 66, 65, 55, 53.8, 53.6, 44, 39, 36.8, 36.5, 30, 25, 24, 21, 18, 0.0, -4.3, -4.7

m.s. 500.2 (AP^+, M+1)

Preparation of (13)

A solution of (11) (0.2g. 0.4 mmol) is acetic acid/water (2:1, 20.8 ml) was heated at 75°C for 5½ hr under nitrogen. The reaction mixture was evaporated under reduced pressure to give an oil which was redissolved in chloroform (30 ml) and washed with sodium bicarbonate solution. The chloroform layer was dried over sodium sulphate, filtered, and the filtrate evaporated to a foam (0.16g). This was crystallised from IPA/Et_2O obtaining (13), 0.057g (37%), m.pt. 126-7°C.

^1H NMR ($CDCl_3$, 400 MHz) δ: 8.3 (m, 1H), 7.26-7.08 (m, 3H), 6.5 (t, 1H, NH), 4.5 (t, 2H), 4.1 (t, 2H), 3.9 (m, 1H), 3.3 (m, 2H), 3.2 (m, 1H), 2.9 (m, 1H), 2.6-2.5 (m, 2H), 2.4 (m, 2H), 2.1 (m, 1H), 1.8-1.3 (m, 10H), 1.26 (d, 3H)

^{13}C NMR ($CDCl_3$) δ: 165, 149, 131, 126, 122, 121, 120.7, 108, 89, 70, 67, 58, 55, 52, 44, 39, 36, 33, 30.4, 29.9, 23, 21

m.s. (386.1, M+1)

R_f 0.5 (SiO_2, 5:1:1 EtOAc : AcOH : NH_4OH)

Method 2

Preparation of (4)

To a mixture of benzyl-2,2,2-trichloroacetimidate (50.6g, 0.2M) and 4-chloro-butan-2-ol (19.8g, 0.18M) in cyclohexane/dichloromethane (2:1, 106.5 ml) at 5°C was added triflic acid (1.2 ml, 0.014M) dropwise with stirring under nitrogen over 30 minutes. There was an immediate precipitate and an exotherm to 30°C. The mixture was cooled to 5°C and stirred for 5 hours, then allowed to warm to room temperature, filtered, the filtrate washed with sodium bicarbonate solution, brine, dried over soium sulphate, filtered and the filtrate evaporated under reduced pressure to give (4) as an oil, 46.4g (128%). This material was used without further purification.

^1H NMR ($CDCl_3$) δ: 7.4-7.2 (m, 5H + $CHCl_3$), 4.5 (AB quartet, 2H), 3.7 (m, 3H), 2.0 (m, 2H), 1.2 (d, 3H).

Impurities observed at δ 4.55 (s, 0.23H), 4.0 (m, 0.08H), 1.4 (s, 2.76H, ≡ 0.23M cyclohexane)

Preparation of (5)

(4) (46.4g) obtained above was added to sodium iodide (68.3g, 0.46M) in acetone (250 ml) and the mixture heated under nitrogen at reflux for 25 hours. Further sodium iodide (14g, 0.09M) dissolved in acetone (50 ml) was added, and the mixture heated under reflux for 16 hours. The reaction mixture was allowed to cool, filtered, the filtrate evaporated under reduced pressure and the residue extracted with hexane (4 x 50 ml). The combined extracts were washed with 1% aqueous sodium thiosulphate solution (2 x 50 ml), water, dried over sodium sulphate, filtered, and evaporated under reduced pressure to give (5) as an oil, 51.9g (98%).

^1H NMR ($CDCl_3$) δ: 7.3 (m, 5H + $CHCl_3$), 4.5 (AB quartet, 2H), 3.62 (m, 1H), 3.25 (m, 2H), 2.0 (m, 2H), 1.25 (d, 3H)

Preparation of (7)

A suspension of *iso*-nipecotamide (18g, 0.14M), anhydrous potassium carbonate (58.2g, 0.42M) and (5) (44.7g, 0.15M) was heated under nitrogen at reflux for 7 hours. The resulting mixture was subjected to hot filtration and the filtrate evaporated under reduced pressure to give a solid. This was redissolved in ethyl acetate, washed with water and brine, and concentrated until crystallization occurred. The solid was

collected by filtration and washed with ethyl acetate and diethyl ether to give (7) 26.1g (64%).

^{1}H NMR ($CDCl_3$) δ: 7.4-7.2 (m, 5H + $CHCl_3$), 5.5 (s, broad, 2H, NH_2), 4.5 (AB quartet, 2H), 3.6 (m, 1H), 2.9 (m, 2H), 2.4 (m, 2H), 2.15 (m, 1H), 2.0-1.6 (m, 8H), 1.2 (d, 3H)

m.s. 291.2 (ES^+, M+1)

Preparation of (9)

To a suspension of $LiAlH_4$ (16.82g, 0.44M) in THF (250 ml) at 5°C was added amide (7) (10.34g, 0.036M) dissolved in THF (150 ml) dropwise over 1 hour. The mixture was allowed to warm to ambient temperature, then stirred for 18 hours under nitrogen. The mixture was cooled to 5°C, aqueous sodium hydroxide solution (7.8M, 33 ml) added dropwise over 30 min, and the mixture filtered through celite. The celite was washed with THF (3 x 50 ml) and the combined filtrate and washings evaporated under reduced pressure to give (9) as an oil, 9.4g (96%).

^{1}H NMR ($CDCl_3$) δ: 7.4-7.2 (m, 5H + $CHCl_3$), 4.5 (AB quartet, 2H), 3.6 (m, 1H), 2.9 (m, 2H), 2.6 (d, 2H), 2.4 (m, 2H), 2.0-1.2 (m, 14H)

m.s. 277.2 (ES^+, M+1)

Preparation of (12)

Trimethylaluminium (2M in toluene, 18 ml) was diluted with toluene (18 ml) and the solution cooled to 0°C. The amine (9) (9.2g, 33 mmol) dissolved in toluene (30 ml) was added over 3 min, followed by SB-224908 (10) (7.6g, 33 mmol). The mixture was heated at reflux for 5 hours, then allowed to cool, and sodium hydroxide solution (10% w/w, 80 ml) added dropwise. The toluene layer was washed with water, brine and evaporated under reduced pressure to give an oil (14.7g). This was purified by flash chromatography on silica (eluting with 0-20% MeOH/CH_2Cl_2) obtaining (12) 9.3g (60%) as an oil.

^{1}H NMR ($CDCl_3$) δ: 8.3 (m,1H), 7.4-7.1 (m,8H + $CHCl_3$), 6.5 (t,1H,NH), 4.5 (m,4H), 4.1 (t,2H), 3.6 (m,1H), 3.3 (t,2H), 3.0 (m,2H), 2.5-2.3 (m, 4H), 2.1-1.6 (m, 7H), 1.5-1.2 (m,5H).

R_f 0.7 (SiO_2, 5:1:1 EtOAc : MeOH : NH_4OH)

Preparation of (13)

(12) (8.2g, 17 mmol) was dissolved in ethanol (150 ml) and glacial acetic acid (8 ml). Oxalic acid dihydrate (2.4g, 19 mmol) was added and the mixture hydrogenated over 10% Pd/C (4.8g) at 45°C, 50 psi for 30 hours. The mixture was allowed to cool, filtered through celite, and the filtrate evaporated under reduced pressure. The residue was partitioned between chloroform (150 ml) and concentrated aqueous potassium

carbonate solution (100 ml). The chloroform layer was washed with water (3 x 25 ml), brine (25 ml), dried over sodium sulphate, filtered, and the filtrate evaporated under reduced pressure to give an oil (4.7g). This was crystallized from *iso*-propanol/diethyl ether obtaining (13) 3g (40%). The product prepared by this method had identical properties to that obtained using Method 1.

5-HT_4 RECEPTOR ANTAGONIST ACTIVITY

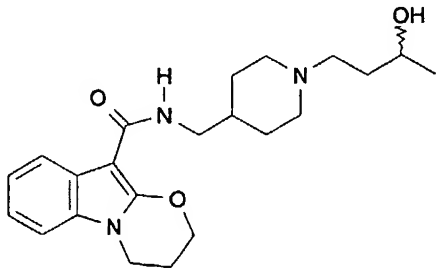
Male Dunkin Hartley guinea-pigs, weighing 200-300g are used. Longitudinal muscle-myenteric plexus (LMMP) preparations, 2-3cm long, are obtained from the distal colon region. These are suspended under a 0.5g load in isolated tissue baths containing Krebs Henseleit solution (NaCl 118mM, KCl 4.7mM KH2PO4 1.2mM MgSO4 7H2O 1.2mM, Glucose 11.1mM, NaHCO3 25mM, CaCl2 6H2O 2.5mM) bubbled with 5% CO_2 in O_2, maintained at 37°C and containing 1uM Granisetron and 0.1uM Methiothepin to block $5HT_3$ and $5HT_1$-like receptors respectively. 100uM Pargyline is also added to the tissues at the start of the experiment. Tissues are left for 15 minutes to equilibrate and then exposed to 5-HT at 0.1uM every 15 minutes until a uniform response is achieved. Following a half hour period for tissues to stabilise, non-cumulative dose response curves to 5-HT are constructed in all tissues. When base-lines have returned to normal, test compounds are added in the reservoirs of the tissue set-ups and washed in to the tissues. Tissues are incubated with the antagonists for 45 minutes after which a second non-cumulative dose response curve to 5-HT is constructed.

To test for selectivity of action, compounds are tested for their ability to antagonise cholinergically-mediated contractions of the guinea-pig colon, evoked by the nicotinic receptor agonist, DMPP (1,1-dimethyl-4-phenyl-piperazinium iodide). For these experiments, tissues and equipment are set up as for the above, $5HT_4$ receptor experiments. After sensitization, non-cumulative dose response curves are constructed to DMPP. Test compounds are incubated with the tissues as above, and a second dose response curve to DMPP created. Results are given as mean pKB ± SEM values for each antagonists.

The compound of formula (I) was found to have a pKB value of 9.3 and did not significantly affect DMPP-evoked contractions.

Claims

1. 3,4-dihydro-*N*-[[1-(3-hydroxybutyl)-4-piperidinyl]methyl]-2*H*-[1,3]oxazino[3,2-*a*]indole-10-carboxamide i.e. the compound of formula (I), or a pharmaceutically acceptable salt thereof:



(I)

2. The compound of formula (I) and its pharmaceutically acceptable salts as claimed in claim 1 in pharmaceutically acceptable form.

3. The compound of formula (I) and its pharmaceutically acceptable salts as claimed in claim 1 or claim 2 in synthetic form.

4. A process for preparing a compound of formula (I) according to claim 1 which comprises reacting 1-(3-(protected)hydroxybutyl)-4-piperidinyl methylamine with methyl 3,4-dihydro-2H-[1,3]oxazino[3,2-a]indole-10-carboxylate and subsequently removing the protecting group.

5. A pharmaceutical composition comprising a compound according to claim 1, and a pharmaceutically acceptable carrier.

6. A compound according to claim 1 for use as an active therapeutic substance.

7 The use of a compound according to claim 1 in the manufacture of a medicament for use as a 5-HT_4 receptor antagonist.

8. The use according to claim 7 for use as a 5-HT_4 antagonist in the treatment or prophylaxis of gastrointestinal disorders, cardiovascular disorders and CNS disorders.

9. A method of treatment of irritable bowel syndrome, gastro-oesophagal reflux disease, dyspepsia, atrial arrhythmias and stroke, anxiety and/or migraine in mammals, such as humans, which comprises the administration of an effective

amount of the compound of the formula (I) or a pharmaceutically acceptable salt thereof.

INTERNATIONAL SEARCH REPORT

Int tional Application No
PCT/EP 99/06780

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D498/04 A61K31/535 //(C07D498/04,C07D209:00,C07D265:00)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 94 10174 A (SMITHKLINE BEECHAM PLC) 11 May 1994 (1994-05-11) claims 1,21-28; example 11	1-9
Y	WO 94 27987 A (SMITHKLINE BEECHAM PLC) 8 December 1994 (1994-12-08) claims 1,8-11	1-9
Y	WO 95 04737 A (SMITHKLINE BEECHAM PLC) 16 February 1995 (1995-02-16) claims 1-14	1-9
Y	WO 93 18036 A (SMITHKLINE BEECHAM PLC) 16 September 1993 (1993-09-16) cited in the application claims 1-15	1-9

-/—

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
19 November 1999	03/12/1999

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax (+31-70) 340-3016	Herz, C

3

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 99/06780

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	L. M. GASTER ET AL.: "N-'1-Butyl-4-piperidinyl)methyl!-3,4-dihydro-2H-'1,3!oxazino'3,2-a!indole-10-carboxamide Hydrochloride: The First Potent and Selective 5-HT(4) Receptor Antagonist Amide with Oral Activity" J. MED. CHEM., vol. 38, no. 24, 1995, pages 4760-4763, XP002123228 table 1	1-9

3

INTERNATIONAL SEARCH REPORT

Information on patent family members

In ational Application No
PCT/EP 99/06780

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9410174 A	11-05-1994	AU 680453 B	31-07-1997
		AU 5419794 A	24-05-1994
		CN 1092422 A	21-09-1994
		EP 0667867 A	23-08-1995
		JP 8502741 T	26-03-1996
		MX 9306844 A	31-01-1995
		NZ 257545 A	29-01-1997
		US 5705498 A	06-01-1998
		ZA 9308204 A	19-08-1994
WO 9427987 A	08-12-1994	AU 693449 B	02-07-1998
		AU 6928394 A	20-12-1994
		CA 2163372 A	08-12-1994
		CN 1126472 A	10-07-1996
		EP 0699194 A	06-03-1996
		JP 8510266 T	29-10-1996
		NZ 267099 A	19-12-1997
		US 5872134 A	16-02-1999
		US 5741801 A	21-04-1998
		ZA 9403493 A	20-11-1995
WO 9504737 A	16-02-1995	AT 172732 T	15-11-1998
		AU 695034 B	06-08-1998
		AU 7609894 A	28-02-1995
		CA 2168750 A	16-02-1995
		CN 1131949 A	25-09-1996
		DE 69414255 D	03-12-1998
		DE 69414255 T	12-05-1999
		EP 0712406 A	22-05-1996
		ES 2125481 T	01-03-1999
		JP 9502168 T	04-03-1997
		NZ 271972 A	27-07-1997
		SI 712406 T	28-02-1999
		ZA 9405773 A	05-02-1996
WO 9318036 A	16-09-1993	AP 401 A	29-08-1995
		AT 180785 T	15-06-1999
		AU 671102 B	15-08-1996
		CA 2131797 A	16-09-1993
		CN 1078471 A,B	17-11-1993
		CZ 9402210 A	13-09-1995
		DE 69325167 D	08-07-1999
		EP 0630376 A	28-12-1994
		EP 0884319 A	16-12-1998
		ES 2132223 T	16-08-1999
		FI 944204 A	12-09-1994
		HU 71121 A	28-11-1995
		IL 105003 A	12-09-1996
		JP 2831467 B	02-12-1998
		JP 7504433 T	18-05-1995
		MX 9301348 A	01-09-1993
		NO 943348 A	09-11-1994
		NZ 249565 A	27-07-1997
		SG 50693 A	20-07-1998
		SI 9300114 A	31-12-1993
		SK 107894 A	12-04-1995
		US 5852014 A	22-12-1998
		ZA 9301709 A	18-01-1994

INTERNATIONAL SEARCH REPORT

Information on patent family members

Int tional Application No
PCT/EP 99/06780

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9318036 A		AU 4081393 A	30-12-1993
		CN 1085083 A	13-04-1994
		EP 0641198 A	08-03-1995
		WO 9324117 A	09-12-1993
		JP 7507290 T	10-08-1995
		MX 9302985 A	01-11-1993
		US 5763459 A	09-06-1998

Form PCT/ISA/210 (patent family annex) (July 1992)